

Amendment to the Claims:

This listing of Claims will replace all prior versions, and listings, of Claims in the application:

Listing of Claims:

- 5 1. (Previously Withdrawn) A method for determining the radiation sensitization potential of a compound, which method comprises:
10 a) introducing a compound to be tested into an aqueous solution comprising a cellular metabolite having a standard biochemical reduction potential more negative than the standard biochemical reduction of oxygen/hydrogen peroxide;
15 b) monitoring the solution for the occurrence of a reaction that produces one or more reactive oxygen species; and
20 c) determining whether the compound has potential radiation sensitization activity, wherein the potential for radiation sensitization activity correlates to the occurrence of a reaction that produces one or more reactive oxygen species.
- 25 2. (Previously Withdrawn) The method of Claim 1 wherein said monitoring of the reaction comprises measuring one or more of: depletion of oxygen, production of hydrogen peroxide, decreased concentration of the cellular metabolite, and production of an oxidation product of the cellular metabolite.
- 30 3. (Previously Withdrawn) The method of Claim 1 wherein said cellular metabolite is selected from the group consisting of ascorbate, NADPH, NADH, FADH and reduced glutathione.
- 35 4. (Previously Withdrawn) The method of Claim 3 wherein said cellular metabolite is ascorbate or NADPH.
- 40 5. (Previously Withdrawn) The method of Claim 1 further comprising the steps of administering one or more compounds so-determined to have potential radiation sensitization activity to a mammalian host bearing a tumor or atheroma or other neoplastic tissue and exposing the tumor or atheroma or other neoplastic tissue to ionizing radiation.

6. (Previously Withdrawn) A method for killing a target cell, which method comprises:

a) administering to said target cell a compound that catalyzes the production of one or more reactive oxygen species from a cellular metabolite having a standard biochemical reduction potential more negative than the standard biochemical reduction of oxygen/hydrogen peroxide; and

b) exposing said cell to ionizing radiation

provided that said compound is not a texaphyrin.

10 7. (Previously Withdrawn) The method of Claim 6 wherein said compound is a porphyrin derivative.

15 8. (Previously Withdrawn) The method of Claim 7 wherein said compound is Fe(III) porphyrin.

15 9. (Previously Withdrawn) A method for killing a tumor cell, which method comprises:

a) selecting a compound determined to have radiation sensitization potential according to the method of Claim 1;

20 b) administering said compound to the tumor cell; and

c) co-administering to the tumor cell a thiol-depleting agent.

25 10. (Previously Withdrawn) The method according to Claim 9 wherein the radiation sensitizing compound a texaphyrin and the thiol-depleting agent is buthionine sulfoximine.

30 11. (Previously Withdrawn) A method of treatment of cancer comprising administering to a patient suffering therewith an effective amount of a texaphyrin radiation sensitizer, an effective amount of a thiol-depleting agent, and an effective amount of ionizing radiation.

12. (Previously Withdrawn) A method for killing a target cell in a tumor, atheroma or other neoplastic tissue, which method comprises:

a) administering to said cell a compound that catalyzes the production of one or more reactive oxygen species from a cellular metabolite having a standard biochemical reduction potential more negative than the standard biochemical reduction of oxygen/hydrogen peroxide;

5 b) co-administering to said cell a second agent selected from the group consisting of DNA alkylators, topoisomerase inhibitors, redox cycling agents, thiol-depleting agents, metabolic inhibitors, and mitochondrial inhibitors; and

10 c) optionally, administering ionizing radiation, provided that where ionizing radiation is not administered, said compound is not a cobalt or iron phthalocyanine or naphthalocyanine when said second agent is ascorbate.

13. (Previously Withdrawn) The method of Claim 12 wherein said second agent is a redox cycling agent.

15 14. (Previously Withdrawn) The method of Claim 13 wherein said redox cycling agent is selected from alloxan, phenazine methosulfate, menadione, doxorubicin, bleomycin and ruthenium (II) tris-(1,10-phenanthroline-5,6-dione).

20 15. (Previously Withdrawn) The method of Claim 14 wherein said redox cycling agent is bleomycin or doxorubicin.

16. (Previously Withdrawn) The method of Claim 12 wherein said second agent is a DNA alkylator.

25 17. (Previously Withdrawn) The method of Claim 12 wherein said second agent is a thiol reducing agent.

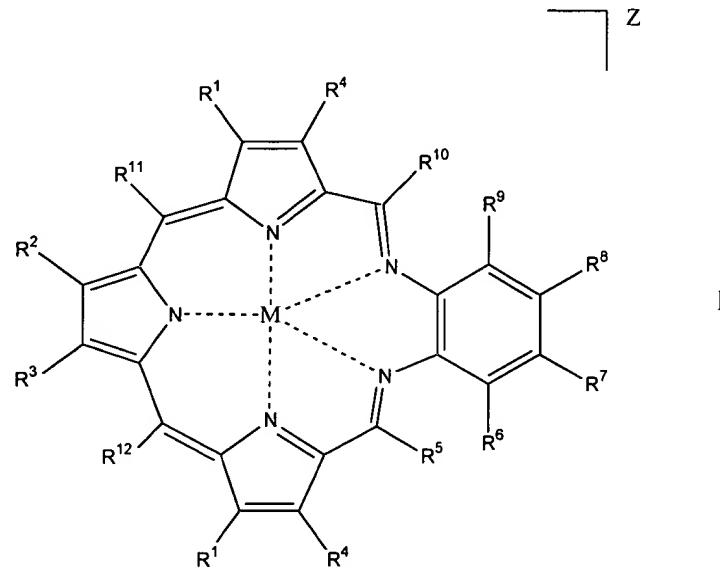
18. (Previously Withdrawn) The method of Claim 17 wherein said thiol reducing agent is buthionine sulfoximine.

30 19. (Previously Withdrawn) The method of any of Claims 12 to 18 wherein said method further comprises exposing the cell to ionizing radiation.

20. (Currently Amended) A method of inducing targeted oxidative stress, in the absence of ionizing radiation, in cells in a mammalian host bearing a tumor or atheroma or other neoplastic tissue, which method comprises:

a) administering to said mammalian host a metal containing texaphyrin of

5 Formula I



wherein M is a divalent metal cation or a trivalent metal cation;

10 R¹ to R⁴ as well as R⁷ and R⁸ are independently selected from the group consisting of hydrogen, carboxyl, carboxylalkyl, acyl, acylamino, aminoacyl, alkyl, substituted alky (particularly hydroxyalkyl or aminoalkyl, and especially where R¹ is hydroxypropyl or aminopropyl), alkenyl, substituted alkenyl, alkoxy, substituted alkoxy, aryl, heteroaryl, heterocyclic, halo, hydroxyl, nitro, and a saccharide;

15 R⁶ and R⁹ are independently selected from the group consisting of hydrogen, carboxyl, carboxylalkyl, acyl, acylamino, aminoacyl, alkyl, substituted alkyl other than iodoalkyl, alkenyl, substituted alkenyl, alkoxy, substituted alkoxy, aryl, heteroaryl, heterocyclic, halo other than iodo, hydroxyl, nitro, and a saccharide;

20 R⁵ and R¹⁰ to R¹² are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkoxy, substituted alkoxy, carboxyl, carboxylalkyl, acyl and acylamino; and

the charge, Z, is an integer having a value less than or equal to 5, an agent

that preferentially accumulates in tumor or atheroma or other neoplastic tissue cells and catalyzes the production of one or more reactive oxygen species from a cellular metabolite having a reduction potential more negative than that of molecular oxygen;

b) optionally, allowing sufficient time for said agent to preferentially accumulate

5 in the cells of the tumor, atheroma or other neoplastic tissue; and

c) administering to said mammalian host a cellular metabolite such as to increase the reactive oxygen species production in the tumor or atheroma or other neoplastic tissue.

10 21. (Original) The method of Claim 20 wherein the reactive oxygen species is catalyzed from ascorbate and ascorbate is administered to said mammalian host.

22. (Withdrawn) The method of Claim 20 wherein the reactive oxygen species is catalyzed from NAD(P)H and NAD(P)H is administered to said mammalian host.

15 23. (Withdrawn) The method according to Claim 20 which method further comprises exposing the tumor or atheroma or other neoplastic tissue to ionizing radiation.

24. (Currently Amended) ~~The method according to any of Claims 20 to 21~~
20 A method of inducing targeted oxidative stress in cells in a mammalian host bearing a tumor or atheroma or other neoplastic tissue, which method comprises:

a) administering to said mammalian host an agent, wherein said agent is motexafin gadolinium or motexafin lutetium or mixtures thereof, that preferentially accumulates in tumor or atheroma or other neoplastic tissue cells and catalyzes the production of one or more reactive oxygen species from a cellular metabolite;

b) optionally, allowing sufficient time for said agent to preferentially accumulate in the cells of the tumor, atheroma or other neoplastic tissue; and

c) administering to said mammalian host a cellular metabolite such as to increase the reactive oxygen species production in the tumor or atheroma or other neoplastic tissue, wherein the reactive oxygen species is catalyzed from ascorbate is administered to said mammalian host.

25. (Previously Withdrawn) A method of treating a mammalian host bearing a tumor or atheroma or other neoplastic tissue comprising administering to that host an effective amount of a combination of motexafin gadolinium and motexafin lutetium and exposing the tumor or atheroma or other neoplastic tissue to ionizing radiation.

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26. (Previously Withdrawn) A pharmaceutical composition comprising effective amounts of motexafin gadolinium and motexafin lutetium, and a pharmaceutically acceptable excipient.

10 27. (Previously Withdrawn) A pharmaceutical composition comprising an agent that preferentially accumulates in cells of a tumor or atheroma or other neoplastic tissue and catalyzes the production of one or more reactive oxygen species from a cellular metabolite having a standard biochemical reduction potential more negative than the standard biochemical reduction of oxygen/hydrogen peroxide, a source or precursor of the cellular metabolite, and a
15 pharmaceutically acceptable excipient.

28. (Newly Added Claim) A method of inducing targeted oxidative stress, in cells in a mammalian host bearing a tumor or atheroma or other neoplastic tissue, which method comprises:

20 a) administering to said mammalian host an agent selected from motexafin gadolinium, motexafin lutetium or mixtures thereof, that preferentially accumulate in tumor or atheroma or other neoplastic tissue cells and catalyzes the production of one or more reactive oxygen species from a cellular metaboite;

25 b) optionally, allowing sufficient time for said agent to preferentially accumulate in the cells of the tumor, atheroma or other neoplastic tissue; and

c) administering to said mammalian host a cellular metabolite such as to increase the reactive oxygen species production in the tumor or atheroma or other neoplastic tissue.